Emerging Life Sciences and Possible Threats to International Security

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Abstract: *At the intersection of emerging technologies and international affairs, one of the most provocative areas is the applications of advanced genetic engineering. The COVID-19 global pandemic and uncertainty about the origin of the causative virus illustrates both immediacy and the potential geopolitical implications of such technologies. These new gene editing techniques include one which has garnered a great deal of attention, the Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) systems, as well as other, less well-known ones. CRISPR is not the first type of gene editing technology, but it is the most well-known within national and international security debates. Such advancements now allow for easier and more tunable manipulation of the genetic code of life with implications for governance of science and technology and with international security significance in the context of proliferation, deterrence, and unconventional weapons. Biosecurity and other emerging technologies require new models, not simple extrapolations of Cold War or more recent deterrence (or nonproliferation) paradigms.*

In the zeitgeist of emerging technologies, new applications and uses are emerging at breakneck speeds. One of the most rapidly advancing, and potentially most profound of these, is advanced gene editing. When thinking about emerging life sciences and biotechnology from an international affairs perspective, considering the future opportunities and security threats that may emerge as science and technology advance is necessary. This includes understanding and analysing the potential physical, political, economic, and human consequences; the probability that competitors will pursue, obtain, or use them; and effects on geopolitical stability.

The potential threats posed by the proliferation of advanced biological technology and knowledge have been emphasized by security scholars who have argued since the late 1990s for the "game changing" and potentially strategic nature of its impact upon security relationships, with accelerating concern in the last decade.[1]

[1] Thomas Preston, *From Lambs to Lions: Future Security Relationships in a World of Biological and Nuclear Weapons* (Boulder, CO: Rowman and Littlefield, 2007); Susan Wright, *Molecular Politics: Developing American and British Regulatory Policy for Genetic Engineering* (Chicago: University of

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Biosecurity concerns range from: resurrecting a virus like the causative agent of small pox; increasing the lethality, duration, or ease of transmission of microbiological agents; and developing novel delivery methods that avoid detection or can overcome preventative measures—like vaccines and other therapeutics.[2] More broadly, scientists are considering whether gene editing techniques like Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) may enable capabilities that challenge nuclear weapons in terms of strategic stability.[3]

The broader biosecurity and nonproliferation communities, along with Congressionally-chartered Committee findings,[4] have recognized that in the twenty-first century, biological weapons are can be (but are not always) cheaper, easier to produce, more widely available, within the capabilities of an increasingly large number of people with access to minimal technical skills and equipment, and more concealable dual-use technologies.[5] The potential synergies between biotechnology and other emerging technologies, such as nanotechnology, big data analytics, and the cognitive neurosciences, not only suggest tremendous potential promise for advancement in technology for consumers and defense applications, but also raise new concerns.[6] Biological weapons are perceived as relatively cheap and accessible, especially when compared to the obstacles involved in obtaining, developing, and deploying nuclear weapons.

With respect to emerging technological capabilities, the range and spectrum of possible capabilities and actors are expanding. In this century, both nation-states and non-state actors may have access to new and potentially devastating dual-use

Chicago Press, 1995); Greg Koblentz, "Pathogens as Weapons: The International Security Implications of Biological Warfare," *International Security,* vol. 28 (2003), pp. 84-122; Susan Martin, "The Role of Biological Weapons in International Politics," *Journal of Strategic Studies,* vol. 25 (2002), pp. 63-98; Francisco Galamas, "Biological Weapons, Nuclear Weapons and Deterrence: The Biotechnology Revolution," *Comparative Strategy,* vol. 27 (2008), pp. 315-323; Kathleen Vogel, *Phantom Menace or Looming Danger? A New Framework for Assessing Bioweapons Threats* (Johns Hopkins University Press, 2013); Margaret E. Kosal, "Anticipating the Biological Proliferation Threat of Nanotechnology: Challenges for International Arms Control Regimes," in Hitoshi Nasu and Robert McLaughlin, eds., *New Technologies and the Law of Armed Conflict* (New York: Springer Academic Press, 2014) pp. 159-174; Margaret E. Kosal, *Nanotechnology for Chemical and Biological Defense* (New York: Springer Academic Press, 2009); and National Research Council of the National Academy of Sciences, *Globalization, Biosecurity, and the Future of the Life Sciences* (National Academies Press, 2006).

[2] Kosal, *Nanotechnology for Chemical and Biological Defense.*

[3] Margaret E. Kosal, "CRISPR & New Genetic Engineering Techniques: Emerging Challenges to Strategic Stability and Nonproliferation," *Nonproliferation Review,* Fall 2020.

[4] *World at Risk: The Report of the Commission on the Prevention of WMD Proliferation and Terrorism*, Dec. 2008, https://www.loc.gov/item/2009373884/.

[5] For this article, "dual use" refers to the fact that almost all the equipment and materials needed to develop dangerous or offensive agents, particularly biological and chemical agents, have legitimate uses in a wide range of scientific research and industrial activity, including defensive military uses. Within this context, it does not refer to the demarcation between civilian and military uses.

[6] Margaret E. Kosal, *Nanotechnology for Chemical and Biological Defense.*

biotechnology.[7] It is a risk that has been highlighted by prominent public figures,[8] policymakers,[9] and other voices.[10] Perhaps most notable, advances in gene editing were included explicitly in the list of threats posed by "weapons of mass destruction and proliferation" by then-U.S. Director of National Intelligence (DNI) James Clapper in the DNI's annual report to Congress in 2016.[11] While detailed examples were not provided by the DNI, the assessment asserted that "[g]iven the broad distribution, low cost, and accelerated pace of development of this [genome editing] technology, its deliberate or unintentional misuse might lead to far-reaching economic and national security implications." Gene editing was the only biotechnology cited by the DNI in the context of threats like the Democratic People's Republic of Korea's nuclear weapons programs, the People's Republic of China's modernization of its nuclear force structure, the Russian Federation's violation of the Intermediate-Range Nuclear Forces (INF) Treaty, the Islamic Republic of Iran's nuclear infrastructure and suspected violation of international agreements, and use of chemical weapons by the Syrian regime and Islamic states terrorists, aka ISIL. In a scholarly context, this article complements prior work on the biosecurity implications of CRISPR, gene editing, and broader issues of biotechnology by international security scholars.[12]

The *nature* of biotechnology—and much of modern science and technology—adds further complications to governance, response, and risk mitigation around the

[7] National Academies of Science, *Biotechnology Research in an Age of Terrorism* (Washington, D.C: National Academies Press, 2004); and National Academies of Science, *Globalization, Biosecurity, and the Future of the Life Sciences* (Washington, D.C.: National Academies Press, 2006).
[8] "Bill Gates warns tens of millions could be killed by bio-terrorism," *The Guardian (UK),* Feb. 18, 2017, https://www.theguardian.com/technology/2017/feb/18/bill-gates-warns-tens-of-millions-could-be-killed-by-bio-terrorism.
[9] "Letter to the President," President's Council of Advisors on Science and Technology, Executive Office of the President, Nov. 2016, https://obamawhitehouse.archives.gov/sites/default/files/microsites/ostp/PCAST/pcast_biodefense_letter_report_final.pdf.
[10] R. G. Reeves, et al., "Agricultural Research, or a New Bioweapon System?" *Science*, vol. 362, no. 6410 (2018), pp. 35-37; Malcolm Dando, "Find the Time to Discuss New Bioweapons," *Nature*, vol. 535 (July 2016), p. 9, https://www.nature.com/news/find-the-time-to-discuss-new-bioweapons-1.20206.
[11] James R. Clapper, Worldwide Threat Assessment of the US Intelligence Community, Statement for the Record to the Senate Armed Services Committee, Feb. 9, 2016, https://www.dni.gov/files/documents/SASC_Unclassified_2016_ATA_SFR_FINAL.pdf
[12] For example, see, Kathleen M. Vogel and Sonia Ben Ouagrham-Gormley, "Anticipating Emerging Biotechnology Threats: A Case Study of CRISPR," *Politics and the Life Sciences,* vol. 37, no. 2 (Fall 2018), pp. 203-219; Gigi Gronvall, "The Security Implications of Synthetic Biology," *Survival,* vol. 60, no. 4 (2018), pp. 165-180*;* Kenneth A. Oye, et al., "Regulating Gene Drives," *Science,* vol. 345, no. 6197 (2014), pp. 626-628; Gregory D. Koblentz, "Pathogens as Weapons: The International Security Implications of Biological Warfare," *International Security,* vol. 29, no. 1 (Winter 2003/2004), pp. 84-122; Caitríona McLeish and Ralf Trapp, "The Life Sciences Revolution and the BWC," *The Nonproliferation Review*, vol. 18, no. 3 (2011), pp. 527-543; and Roger Roffey and Chandré Gould, "Preventing the Misuse of the Life Sciences," *The Nonproliferation Review*, vol. 8, no. 3 (2011), pp. 557-569.

globe. Biotechnology is a dual-use technology, meaning that the same or similar techniques, manufacturing elements, and processes used for beneficial purposes could also be misused for deleterious purposes. Relatedly, some basic and applied research is considered dual-use research of concern.[13] Advances in biotechnology and gene editing specifically not only potentially pose security and proliferation concerns, but they also may enable new capabilities for defense, detection, and verification of biological agents. In addition, there may well be diagnostic capabilities for emerging infectious diseases, like COVID-19,[14] and multiple other beneficial outcomes beyond therapeutic gene editing.

Gene Editing

Gene editing is the ability to make changes, splice DNA at certain locations within the genetic material. Gene editing technology can be combined with other innovations, such as advanced data analytics (like machine learning and artificial engineering), nanotechnology, the cognitive sciences, and information and communications technologies (aka cyber-everything) to further applications and capabilities.

In modern history, gene editing or genetic modification came to fruition in the early 1970s[15] and was significantly advanced in the 1980s through the invention of techniques like polymerase chain reaction (PCR), which enabled the production of

[13] "United States Government Policy for Institutional Oversight of Life Sciences Dual Use Research of Concern," DEPARTMENT, Sept. 24, 2015, http://www.phe.gov/s3/dualuse/Documents/durc-policy.pdf.

[14] "SHERLOCK Team Advances Its CRISPR-Based Diagnostic Tool," Broad Institute, Oct. 4, 2019, https://www.broadinstitute.org/news/sherlock-team-advances-its-crispr-based-diagnostic-tool; "Enabling coronavirus detection using CRISPR-Cas13: An open-access SHERLOCK research protocol," McGovern Institute, Feb. 14, 2020, https://mcgovern.mit.edu/2020/02/14/enabling-coronavirus-detection-using-crispr-cas13-an-open-access-sherlock-research-protocol/; and Sabbi Lall, "SHERLOCK-based one-step test provides rapid and sensitive COVID-19 detection," McGovern Institute, May 5, 2020, https://mcgovern.mit.edu/2020/05/05/sherlock-based-one-step-test-provides-rapid-and-sensitive-covid-19-detection/.

[15] Kathleen Danna and Daniel Nathans, "Specific Cleavage of Simian Virus 40 DNA by Restriction Endonuclease of Hemophilus Influenzae," Proceedings of the National Academy of Sciences of the United States of America, vol. 68, no. 12 (Dec. 1971), pp. 2913–2917, https://www.pnas.org/content/68/12/2913; David A. Jackson, Robert H. Symons, and Paul Berg, "Biochemical Method for Inserting New Genetic Information into DNA of Simian Virus 40: Circular SV40 DNA Molecules Containing Lambda Phage Genes and the Galactose Operon of Escherichia coli," *Proc National Academy of Science*, vol. 69, no. 10 (1972), pp. 2904–2909, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC389671/; and Stanley N. Cohen and Annie C. Y. Chang, "Recircularization and Autonomous Replication of a Sheared R-Factor DNA Segment in Escherichia coli Transformants," *Proc National Academy Science*, vol. 70, no. 5 (May 1973), pp. 1293–1297, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC433482/.

large amounts of identical genetic material.[16] These early gene editing techniques required—and to some extent still do require—significant expertise and tacit knowledge, and access to advanced facilities and equipment. The techniques were time-consuming (months to years), expensive, and subject to error at multiple steps.

Among the most recent additions to the genome-editing arsenal is CRISPR, a bacteria-derived system that uses RNA molecules that recognize specific human DNA sequences.[17] CRISPR is associated with specific enzymatic proteins, such as Cas9. The RNA acts as a guide, matching the enzyme—gene-scale scissors, effectively—to corresponding locations on a gene. Once found, the guide RNA directs the enzyme to cut the DNA. What is so groundbreaking in this discovery is that the enzyme is programmable and can be directed to cut any specific part of the DNA. CRISPR harnesses naturally occurring processes within bacteria and redirects this bacterial immune system response to essentially cut and paste segments of DNA at desired location within a genetic sequence. CRISPR-Cas9 is among the simplest genome-editing tools to use because it relies on RNA-DNA base-pairing rather than designing and synthesizing particular proteins that bind specific DNA sequences. Since 2015, at least two technically simpler techniques than CRISPR-Cas9 have been reported: families of smaller Cas enzymes, SaCas9[18] and Cas12,[19] as well as other Cas enzymes systems.[20] In 2019, the use of CRISPR for editing of an entire chromosome was demonstrated, which the study's authors assert may enable "precise, rapid, large-scale genome engineering operations [that] are useful tools for creating diverse synthetic genomes."[21] From a security and governance perspective, there is no single gene editing technology on which to focus.

In fact, there are two distinct types of gene editing: somatic and germline. Somatic gene editing affects mature cells in an organism and is not carried forward in future generations of people. Most gene therapies historically have been of this type, e.g., treatment of genetic diseases like hemophilia, immune deficiencies, and some

[16] Randall K. Saiki, et al., "Enzymatic amplification of beta-globin genomic sequences and restriction site analysis for diagnosis of sickle cell anemia," *Science,* vol. 230, no. 4732 (1985), pp. 1350–1354, https://science.sciencemag.org/content/230/4732/1350.

[17] For an excellent overview of the CRISPR-Cas9 system by two of the technique's discovers, see, Jennifer A. Doudna and Emmanuelle Charpentier, "The new frontier of genome engineering with CRISPR-Cas9," *Science*, vol. 346, no. 6213 (Nov. 2014), pp. 1077-1088, https://science.sciencemag.org/content/346/6213/1258096.

[18] F. Ann Ran, et al., "In vivo genome editing using Staphylococcus aureus Cas9," *Nature*, vol. 520 (April 2015), pp. 186-191.

[19] Bernd Zetsche, et al. "Cpf1 Is a Single RNA-Guided Endonuclease of a Class 2 CRISPR-Cas System," *Cell,* vol. 163, no. 3 (Oct. 2015), pp. 759-771; and Ines Fonfara, et al., "The CRISPR-associated DNA-cleaving enzyme Cpf1 also processes precursor CRISPR RNA," *Nature,* vol. 532 (April 2016), pp. 517-521.

[20] Su Bin Moon, et al., "Recent Advances in the CRISPR genome editing tool set," *Experimental & Molecular Medicine,* vol. 51 (2019), pp. 1-11.

[21] Kaihang Wang, Daniel de la Torre, Wesley E. Robertson, and Jason W. Chin, "Programmed chromosome fission and fusion enable precise large-scale genome rearrangement and assembly, *Science*, vol. 365, no. 6456, (Aug. 30, 2019), pp. 922-926.

cancers.[22] While CRISPR has received the most attention, another gene editing system—Zinc Finger Nucleases (ZFN)—has progressed further in clinical applications, including treatment of sickle-cell disease,[23] antitrypsin deficiency, Parkinson's disease, and others.[24] Somatic gene editing technologies are in the early stages of translational and clinical biomedical research, but they are expected to play an increasing role in the field and medical applications. In contrast, germline editing specifically aims to change the inheritable DNA that will be passed to an organism (or person's) progeny.[25] Human germline editing is banned in the United States, many European nations, and other states.[26]

Successful germline editing has been performed in animal models such as fish, rats, cattle, sheep, and pigs.[27] In one example, germline editing was used to modify embryonic development of the neural crest (NC) in amphibians, and these modifications were observed in approximately 22 percent of the resulting animals.[28] The mutations were also passed to the next generation of offspring. The NC is a unique cell population that are pluripotent, i.e., they can give rise to several different cell types and are highly migratory. The neural crest cells form a variety of cell types,

[22] Cynthia E. Dunbar, Katherine A. High, J. Keith Joung, Donald B. Kohn, Keiya Ozawa, and Michel Sadelain, "Gene therapy comes of age," *Science*, vol. 359, no. 6372 (Jan. 12, 2018), https://science.sciencemag.org/content/359/6372/eaan4672.
[23] Matthew Porteus, "Mammalian Gene Targeting with Designed Zinc Finger Nucleases," *Molecular Therapy,* vol. 13 (2006), pp. 438-446.
[24] Mansilla-Soto, Jorge; Riviere, Isabelle; Boulad, Farid; et al., "Cell and Gene Therapy for the Beta-Thalassemias: Advances and Prospects," *Human Gene Therapy,* vol. 27, no. 4 (April 2016), pp. 295-304; and Young-Il Jo, Hyongbum Kim, and Suresh Ramakrishna, "Recent developments and clinical studies utilizing engineered zinc finger nuclease technology," *Cellular and Molecular Life Sciences,* vol. 72, no. 20 (Oct. 2015), pp. 3819-3830.
[25] Rebecca A. Lea and Kathy K. Niakan, "Human germline genome editing," *Nature Cell Biology*, vol. 21 (2019), pp. 1479–1489, https://www.nature.com/articles/s41556-019-0424-0.
[26] I. Glenn Cohen and Eli Y. Adashi, "The FDA is prohibited from going germline," *Science*, vol. 353, no. 6299, (Aug. 5, 2016), pp. 545-546, https://science.sciencemag.org/content/353/6299/545.
[27] Aaron McKenna, et al., "Whole organism lineage tracing by combinatorial and cumulative genome editing," *Science,* vol. 353, no. 6298 (Jul 29, 2016), pp. 462-475, https://science.sciencemag.org/content/353/6298/aaf7907; K. Yoshimi, T. Kaneko, B. Voigt, and T. Mashimo, "Allele-specific genome editing and correction of disease-associated phenotypes in rats using the CRISPR-Cas platform," *Nature Communications,* vol. 5, no. 4240 (2014), pp. 1-9; YoungTae Heo, et al., "CRISPR/Cas9 Nuclease-Mediated Gene Knock-In in Bovine-Induced Pluripotent Cells," *Stem Cells Dev,* vol. 24 (2015), pp. 393-402; Hongbin Han, et al., "One-step generation of myostatin gene knockout sheep via the CRISPR/Cas9 system," *Frontiers of Agricultural Science and Engineering,* vol. 1 (2014), pp. 2-15; and Qianqian Kang, et al., "Improving pig genetic resistance and muscle production through molecular biology," in 10th World Congress on Genetics Applied to Livestock Production, 2014, https://asas.org/docs/default-source/wcgalp-proceedings-oral/362_paper_10607_manuscript_1526_0.pdf.
[28] Zhongzhen Liu, et al., "Efficient genome editing of genes involved in neural crest development using the CRISPR/Cas9 system in Xenopus embryos," *Cell & Bioscience,* vol. 6, no. 22 (2016), https://cellandbioscience.biomedcentral.com/articles/10.1186/s13578-016-0088-4.

including the peripheral nervous system and face bones. This application illustrates how gene editing bridges and expands potential applications into the cognitive neurosciences, another area of emerging technology.

Unsuccessful modification of human germline was first reported in 2015.[29] A group of Chinese scientists reported using CRISPR-Cas9 gene editing techniques to modify human embryos. Their paper, published in the Chinese journal *Protein & Cell*, came as little surprise to the scientific community, but it renewed debate about what types of gene editing research should be performed and how potentially to limit this research. The article describes how scientists, based in Guangzhou, used the CRISPR-Cas9 system to cut DNA in human embryos and then attempted to repair it by introducing new DNA.[30] The team reportedly used non-viable embryos obtained from fertility clinics, in which the eggs had been modified so that these experiments would not result in a live birth. The article also raises questions about the appropriate way to disseminate such experimental work.

In November 2018, Chinese scientist He Jiankui announced that twin baby girls had been born after he used CRISPR to edit the DNA of two human embryos, which were successfully carried to term after re-implantation in the mother's body.[31] This work garnered significant attention because the gene editing that He and his team performed affected the germline. In other words, the modification introduced can be carried on to children that the two girls, reportedly named Lulu and Nana, might have in the future. Less well known is the fact that He reported that another Chinese woman is pregnant with a CRISPR gene-edited embryo, which has been confirmed tacitly.[32]

As of May 2020, the experimental procedure and results claimed by He have not been verified, nor have they been subjected to intensive scientific review (separate from legal and ethical review). Based on what He has released publicly, it appears that the editing process was not as precise as initially described, i.e., "off-target" mutations, when a different part of the gene than intended is altered, were observed among other technical criticisms.[33] While CRISPR has been lauded for its specificity (compared to other techniques), off-target or "promiscuous" behavior by CRISPR-Cas9 has been reported.[34] For example, in developing gene-based treatments for sickle cell disease,

[29] Puping Liang, et al., "CRISPR/Cas9-mediated gene editing in human tripronuclear zygotes," *Protein & Cell,* vol. 6, no. 5 (May 2015), pp. 363-372.

[30] David Cyranoski and Sara Reardon, "Embryo editing sparks epic debate," *Nature*, vol. 520, (Apr. 2015), pp. 593-595.

[31] Dennis Normile, "Shock greets claim of CRISPR-edited babies," *Science,* vol. 362, no. 6418 (Nov. 2018), pp. 978-979.

[32] "He Jiankui: China condemns 'baby gene editing' scientist," *BBC News,* Jan. 21, 2019, https://www.bbc.com/news/world-asia-46943593.

[33] Haoyi Wang and Hui Yang, "Gene-edited babies: What went wrong and what could go wrong," *PLOS Biology,* April 30, 2019, https://journals.plos.org/plosbiology/article?id=10.1371/journal.pbio.3000224.

[34] Henriette O'Green, Abigail S. Yu, and David J. Sega, "How specific is CRISPR/Cas9 really?" *Current Opinion in Chemical Biology,* vol. 29 (2015), pp. 72-78; Shengdar Q. Tsai, et al., "GUIDE-seq enables genome-wide profiling of off-target cleavage by CRISPR-Cas

there is concern about unwanted edits in tumor suppressor genes, which could lead to leukemia.[35] Researchers need to be aware of gene sequences that may unintentionally be effected by the techniques. While significantly easier compared to early gene editing techniques, it is not trivial,[36] contrary to what some scientists assert. In the context of international security, certain claims of capabilities are hard to verify and therefore increase uncertainty.

Subsequent research by scientists unassociated with the Chinese researchers found that the mutation that He and his team claimed they performed correlate with increased mortality.[37] Earlier work has also shown that the edited gene has a role in memory and cognition,[38] which has led some to speculate that it might lead to human enhancements.[39] These observations are another example of where advanced gene editing intersects with another area of emerging science and technology, the cognitive neurosciences and their applications.

Exemplifying the present reality that scientific research is not unique to any single nation, Russian scientist Denis Rebrikov announced that he was pursuing similar gene editing experiments. Furthermore, he said that he intended to use CRISPR for germline editing of humans in June 2019. Months later, he re-iterated that intent.[40]

Concern regarding norms of conduct with respect to advanced biotechnology is further reflected in some of Russia's other behavior, including the use of unscheduled, military-grade nerve agents against Sergei Skripal and his daughter, Yulia Skripal, former government affiliates, who were living in the United Kingdom at the time. If Russia is pursuing broader efforts to erode the post-WWII liberal international order, of which the Skripal case arguably is exemplar, the Russian scientists' announcement would be further illustrative. Alternatively, Rebrikov could be an individual scientist sending up a test balloon to see how Russian President Vladimir

nucleases," *Nature Biotechnology,* vol. 33 (2015), pp. 187-197; and Jennifer E. Chapman, David Gillum, and Samira Kiani, "Approaches to reduce CRISPR off-target effects for safer genome editing," *Applied Biosafety: Journal of ABSA International*, vol. 22, no. 1 (2017), pp. 7-13.

35 Dana Carroll, "Collateral damage: benchmarking off-target effects in genome editing," *Genome Biology*, vol. 20 (2019), pp. 114-116.

36 Jon Cohen, "One of our reporters tried to do CRISPR. He failed miserably," *Science,* Nov. 3, 2016. https://www.sciencemag.org/news/2016/11/one-our-reporters-tried-do-crispr-he-failed-miserably.

37 Xinzhu Wei and Rasmus Nielsen, "CCR5-Δ32 is deleterious in the homozygous state in humans," *Nature Medicine,* vol. 25 (June 2019), pp. 909-910.

38 Miou Zhou, et al., "CCR5 is a suppressor for cortical plasticity and hippocampal learning and memory," *eLife,* vol. 20, no. 5 (Dec. 2016), https://elifesciences.org/articles/20985; and Mary T. Joy, et al., "CCR5 Is a Therapeutic Target for Recovery after Stroke and Traumatic Brain Injury," *Cell,* vol. 176, no. 5 (Feb. 2019), pp. 1143-1157.

39 Antonio Regalado, "China's CRISPR twins might have had their brains inadvertently enhanced," *MIT Technology Review*, Feb. 21, 2019, https://www.technologyreview.com/s/612997/the-crispr-twins-had-their-brains-altered/.

40 David Cyranoski, "Russian biologist plans more CRISPR-edited babies," *Nature,* June 10, 2019, https://www.nature.com/articles/d41586-019-01770-x; and Jon Cohen, "Embattled Russian scientist sharpens plans to create gene-edited babies," *Science,* Oct. 21, 2019, https://www.sciencemag.org/news/2019/10/embattled-russian-scientist-sharpens-plans-create-gene-edited-babies.

Putin responds. Regardless, the demonstrated interest and intent to use CRISPR gene editing techniques is ongoing and not limited to any single nation-state.

Intersection of Modern Biotechnology and Security

From a pre-CRISPR-era, a gene editing experiment with implications for advanced bioweapons and the hypothetical capability to cause catastrophic death was demonstrated in what came to be known as the Australian Mouse Pox Experiment. In a 2001 publication, a gene known to suppress the immune system was spliced into a contagious virus creating a strain so powerful that it killed even those mice inoculated against the virus. A team of scientists initially inserted a protein involved in immune response, Interleukin-4 (IL-4), and mouse egg protein into the mouse pox virus with the goal of triggering an immune response against mouse eggs to make the animals infertile.[41] As hypothesized, the animals became infertile; however, the modified virus also suppressed normal anti-viral cell-mediated cytokine responses—meaning that the animals' livers were destroyed and approximately half of the mice died, even though they had previously been vaccinated against mouse pox. Previously, IL-4 had been observed to cause increased pathogenicity in some viruses (e.g., influenza), but not in others. In hindsight, the question was raised: should the result have been anticipated? From an international security perspective, it illustrates how much uncertainty exists.

The work was subsequently repeated by a different, independent team of scientists as part of an effort to develop a countermeasure. In this iteration, all of the mice died.[42] The scientific team reportedly observed similar results with cow pox, which can infect humans, and rabbit pox viruses.[43] The latter work has been presented at scientific conferences, but it has not been published in open research literature. Given that the results of the mouse pox experiment were known, why the researchers moved forward to repeat with a virus that more closely resembles smallpox prompts concerns regarding how basic research is done. Unintentionally creating biological agents with lethality greater than found in nature or that can avoid existing countermeasures must be avoided.

The mouse pox IL-4 experiments illustrate conceptually how pathogenicity or other characteristics of a microorganism could be changed in the deleterious manner. In addition to the increased lethality, these experiments were concerning for potential implications to create a strain of the human variant of the smallpox virus that could be resistant to the vaccine. Vaccines are part of deterrence by denial strategies, in that they make an attack with such an agent unsuccessful, thereby reducing incentive for an

[41] R.J. Jackson, et al., "Expression of Mouse Interleukin-4 by a Recombinant Ectromelia Virus Suppresses Cytolytic Lymphocyte Responses and Overcomes Genetic Resistance to Mousepox," *J Virol,* vol. 75 (2001), pp. 1,205-1,210.
[42] Nanhai Chen, et al., "Poxvirus interleukin-4 expression overcomes inherent resistance and vaccine-induced immunity: Pathogenesis, prophylaxis, and antiviral therapy," *Virology,* vol. 409, no. 2 (Jan. 2011), pp. 328-337.
[43] Debora MacKenzie, "US develops lethal new viruses," *New Scientist,* Oct. 29, 2003, https://www.newscientist.com/article/dn4318-us-develops-lethal-new-viruses/.

attacker to do so. The concern is that advanced gene editing techniques can enable easier and more widespread manipulation of microbiologicals for malfeasant intentions to use as biological weapons or bioterrorist agents.

From an experimental design and operational perspective, these experiments are far from technically or operationally exact "recipes" for extrapolation to human systems. The mouse pox experiments were performed using traditional laborious techniques. The potential for creativity in this respect shouldn't be dismissed, but also should not be over-hyped.

Advanced Gene Editing for Nonproliferation, Verification, and Arms Control

As mentioned above, biotechnology is dual use, that is techniques and processes that are used to create beneficial uses, such as vaccines, yet are often the same or similar to the techniques and processes that could be use create weaponized biological (or chemical) agents. Much of gene editing falls into the area of basic and applied research. This exploration is called Dual-Use Research of Concern (DURC) and is defined as "research that, based on current understanding, can be reasonably anticipated to provide knowledge, information, products, or technologies that could be directly misapplied to pose a significant threat with broad potential consequences to public health and safety, agricultural crops and other plants, animals, the environment, materiel, or national security."[44]

For example, this technology, originating in CRISPR, has been applied to new systems that can mitigate the harms of biological weapons. Rooted in gene editing technology, SHERLOCK and DETECTR, are "cousins" of CRISPR.[45] This technique can be used to show the presence or lack of the genetic signature, such as by a virus, in a design inspired by ELISA tests like a simple home pregnancy test.[46] The potential applications of this technology extend to in-field testing, public health, and biodefense.[47] The emergence of SHERLOCK and DETECTR technology

[44] "United States Government Policy for Institutional Oversight of Life Sciences Dual Use Research of Concern," Washington, D.C., Sept. 24, 2015, http://www.phe.gov/s3/dualuse/Documents/durc-policy.pdf.
[45] Janice S. Chen, et al., "CRISPR-Cas12a target binding unleashes indiscriminate single-stranded DNase activity," *Science*, vol. 360, no. 6387 (April 27, 2018), pp. 436-439, https://science.sciencemag.org/content/360/6387/436; and Jonathan S. Gootenberg, et al., "Nucleic acid detection with CRISPR-Cas13a/C2c2," *Science*, vol. 356, no. 6336 (April 28, 2017), pp. 438-442, https://science.sciencemag.org/content/356/6336/438.
[46] Jonathan S. Gootenberg, et al., "Multiplexed and portable nucleic acid detection platform with Cas13, Cas12a, and Csm6," *Science*, vol. 360, no. 6387 (April 27, 2018), pp. 439-444, https://science.sciencemag.org/content/360/6387/439; and Cameron Myhrvold, et al., "Field-deployable viral diagnostics using CRISPR-Cas13," *Science*, vol. 360, no. 6387 (April 27, 2018), pp. 444-448, https://science.sciencemag.org/content/360/6387/444.
[47] Dipali G. Sashital, "Pathogen detection in the CRISPR–Cas era," *Genome Med,* vol. 10, no. 32 (2018), https://doi.org/10.1186/s13073-018-0543-4; and Daniel S. Chertow, "Next-generation diagnostics with CRISPR," *Science*, vol. 360, no. 6387 (April 27, 2018), pp. 381-382, https://science.sciencemag.org/content/360/6387/381.

potentially addresses one of the threats of biological weapons, that is, their capacity to remain undetected and anonymous.

It would be overly optimistic to suggest that the advances of SHERLOCK and DETECTR technology solve the problems that the world faces with biodefense or other emerging infectious diseases like COVID-19. Bottom line: those are political problems rather than technological ones. The threat of powerful biological agents still remains and has only grown given the advancements in the ways that we can essentially code deadlier, more resilient biological agents. Yet, the strongest defense against biological weaponry is prevention. Human capabilities have increased over time with improved detection and diagnostics, and technologies like SHERLOCK and DETECTR may further those capabilities substantially, through enabling faster and more precise detection of emerging infectious diseases or ones that came about through human intervention.

International Governance Challenges

Reducing the risk from state-based misuse of biotechnology for biological proliferation will mean considering the highly transnational nature of biotechnology research and development. In order to reduce the risk of malfeasant application of technology, traditional and innovative new approaches to nonproliferation and counterproliferation are important policy elements considerations to reduce the risk of malfeasant application of technology.

Robust international agreements lower the risk of terrorist applications by eliminating legal routes for states and terrorists to obtain agents, precursors, or weaponization materials. Additionally, they also can minimize possible transfers from state to non-state actors through theft, deception, or other means through monitoring and verification of materials protection, control, and accountability efforts and establishment of legal norms. Efforts to strengthen the international regime to control transfers of dual-use materials and equipment are also important. To reduce the risk of misusing biotechnology for weapons, the highly transnational nature of biotechnology research and development is a major consideration. For example, the U.S. National Science Advisory Board for Biosecurity (NSABB) notes, "Synthetic genomics technology is globally distributed and used by scientists worldwide. Yet, not all countries recognize the dissemination of synthetic genomics research and technology as an issue of global biosecurity concern, which could limit the effectiveness of domestically-led strategies."[48] Similar concerns apply to gene editing technologies.

Biological weapons verification faces a litany of challenges, from the technical to the policy level.[49] The risks associated with traditional biological weapons have not

[48] David Relman, "Working Group on Synthetic Genomics: Progress Report," Presentation to the National Security Advisory Board for Biosecurity meeting, July 13, 2006, http://www.biosecurityboard.gov.

[49] Amy E. Smithson, "Tall Order: Crafting a Meaningful Verification Protocol for the Biological Weapons Convention," *Politics and the Life Sciences,* vol. 18, no. 1 (March 1999), pp. 79-85; Jez Littlewood, *The Biological Weapons Convention: A Failed Revolution* (Aldershot: Ashgate

been extinguished. Rather biological weapons, like *Bacillus anthracis,* the causative agent of anthrax, remain perhaps the greatest risk. Relatedly, the mid-twentieth century capabilities have arguably diffused the furthest. While nuclear weapons have their own challenges, they can be counted, and nuclear weapons proliferation can be detected and verified more easily as compared with verification in the biological (and chemical) realms. Advanced biotechnologies already present new compliance challenges. Many times, it's less the specific technologies and rather surrounding geopolitical and economic uncertainties that affect their use.

Regulations, authorities, and norms vary greatly across states, which makes basic international cooperation and governance of these issues difficult. These are complex issues even before one considers the challenges of language, culture, intentions, signaling, and perceptions. The majority of states internationally lack explicit legislation permitting or forbidding genetic engineering in humans. Most states consider such research experimental and not therapeutic. However, in nations with policies regarding inheritable genetic modification, the practice has been prohibited by law or other regulatory mechanisms. A consensus is most visible in Western Europe, where 15 of 22 nations prohibit the modification of the germ line.[50] The U.S. National Institutes of Health's Recombinant DNA Advisory Committee explicitly states that it "will not at present entertain proposals for germ line alterations, but will consider proposals involving somatic cell transfer."[51]

Following the controversy around Chinese scientist He's announcement of using CRISPR for human germline editing, Chinese Chairman Xi Jinping called for new domestic regulations on gene editing: "Technology involving gene editing, gene transfer and gene regulation would be categorized as 'high-risk' and placed under the authority of the State Council, China's cabinet."[52] Such categorization would be equivalent to or potentially even more restrictive than similar federal regulations in the United States, i.e., what's known as the Select Agent Rules.

Publishing, 2005); Nicholas A. Sims, "Toward the BWC Review Conference: Diplomacy Still in the Doldrums," *Disarmament Diplomacy*, no. 82 (Spring 2006), http://www.acronym.org.uk/old/dd/dd82/82ns.htm; Filippa Lentzos, "Hard to Prove," *The Nonproliferation Review*, vol. 18, no. 3 (2011), pp. 571-582; John Hart and Ralph Trapp, "Science, Technology, and the Biological Weapons Convention," *Arms Control Today,* vol. 42, no. 8 (Oct. 2012), pp. 15-21; Roger Roffey and Chandré Gould, "Preventing the Misuse of the Life Sciences," *The Nonproliferation Review*, vol. 18, no. 3 (2011), pp. 557-569; and Jean Pascal Zanders and Amy Smithson, "Creating a More Robust BWC Regime: A Time for Action," *The Nonproliferation Review,* vol. 18, no. 3 (2011), pp. 583-590.

[50] Motoko Araki and Tetsuya Ishii, "International regulatory landscape and integration of corrective genome editing into in vitro fertilization," *Reproductive Biology and Endocrinology,* vol. 12, no. 108 (2014), http://www.rbej.com/content/12/1/108.

[51] "NIH Guidelines for research involving recombinant or synthetic nucleic acid molecules," National Institutes of Health Recombinant DNA Advisory Committee (NIH-RAC), April 2016, http://osp.od.nih.gov/office-biotechnology-activities/biosafety/nih-guidelines; and Terence R. Flotte, "Therapeutic Germ Line Alteration: Has CRISPR/Cas9 Technology Forced the Question?" *Human Gene Therapy,* vol. 26, no. 5 (May 2015), pp. 245-246.

[52] David Cyranoski, "China set to introduce gene-editing regulation following CRISPR-baby furore," *Nature,* May 20, 2019, https://www.nature.com/articles/d41586-019-01580-1.

The information revolution and globalization have made new technological developments accessible and relatively inexpensive to many nations. Advances in biotechnology and information technology have been driven by the need for improved biomedical products, public health, or industrial applications. Perhaps one of the most significant aspects of gene editing is the fact that it amplifies the abilities of existing technologies, a phenomenon that has not gone unnoticed by the international community. Advanced analytics, the internet, and other communication leaps have led to much greater visibility into the availability and potential for technology—particularly in the context of biotechnologies—to be misused for deleterious purposes.[53] The advances in the convergence of advanced biology with information sciences in the form of big data analytics may take this impact even further. The advances also might change the time scale under which current security and threat environments may be altered. These advances also have fostered the proliferation of knowledge, as well as spurred interest in the creation of novel non-traditional uses of advanced technology. Without an active and diverse Scientific Advisory Board (SAB) or institutionalized means to provide advice on emerging technologies with implications for biological proliferation, a verification protocol appended to a traditional arms control regimes might well become an artifact of, at best, late twentieth century microbiology and engineering. Because gene editing is well-suited for technology convergence, its implications extend far beyond the field of genomes.

The most effective institution to verify twenty-first century challenges of biological weapons proliferation is unlikely to resemble the dominant—and still valuable and relevant—institutions of Cold War-era weapons verification. The biological weapons nonproliferation community should continue to learn from this model. However, the international community should not rely too heavily on this verification institution for securing any emerging technology, biological or otherwise.

Modeling approaches for limiting biological weapons proliferation too closely to those used to limit nuclear weapons can be perilous and has been discussed previously.[54] Compared to nuclear security, securing and safeguarding fissile material is a reasonable goal. Key characteristics of the ingredients, notably the distinct uses of highly enriched uranium, the origin of the substance, and the technologies associated with the processes. Too often, policymakers have been pressured to incorporate approaches to biological agents under the auspices of strategies associated with nuclear weapons, particularly regarding material control. Yet this response undermines and simplifies many distinct and differing characteristics of biological agents and nuclear material. One such method often attempted in this regard is a focus upon pathogen

[53] *National and Transnational Security Implications of Big Data in the Life Sciences*, report prepared by the American Association for the Advancement of Science (AAAS) in conjunction with the Federal Bureau of Investigation (FBI) and the United Nations Interregional Crime and Justice Research Institute, Nov. 10, 2014, http://www.aaas.org/sites/default/files/AAAS-FBI-UNICRI_Big_Data_Report_111014.pdf. The author served as an expert as part of the FBI-AAAS working group.

[54] Marc Ostfield, "Pathogen Security: The Illusion of Security in Foreign Policy and Biodefense," *International Journal of Risk Assessment and Management,* vol. 12 (2009), pp. 204-221.

security or securing and denying access to the materials necessary in developing biological weapons. Those same characteristics that make nuclear weapons amenable to tracking are what make biological weapons material difficult to monitor and verify. These characteristics include presence in nature, production costs, diversity of material, and other legitimate uses. Other than smallpox and one other infectious disease (rinderpest), all other microbiologicals are found in nature. With gene synthesis techniques, the code of the DNA (or RNA) sequence alone may be used to create a virus from "scratch."[55] Widespread, international publication means that knowledge about advances in science and technology are widely available, and may be digital (rather than physical). Due to gene sequence data (i.e., code) and synthesis capabilities, samples may never be transported. There may not be "bugs" to lock up, even if it were possible (it's not). While many active members of the biosecurity and biological nonproliferation communities recognize this, it is not that unusual to still find proposals that are essentially a biological agent's variation on nuclear 'Materials, Protection, Control, and Accountability' programs. The organizational structure and approaches to limiting proliferation and harm from emerging biotechnologies should learn from, but not be wedded to, nuclear models.

Rather than focusing on securing biological materials and laboratories from misuse, other recommendations and programs may be more effective. These recommendations include: bio-surveillance and early detection capabilities along with global laboratory and research cooperation—a twentieth-first century extension of the Nunn-Lugar Cooperative Threat Reduction programs.[56] An effective verification regime for reducing the threat of biological weapons at present is more likely to resemble an intelligence activity than a traditional arms control agency. Monitoring and analyses will be of critical importance. The structure of an institution intended to take on the potential full scope of biotechnology must be able to absorb and respond to uncertainties to be most effective. This is particularly the case if it is to have a deterrent effect with respect to potential proliferators. While the Biological Weapons Convention (BWC) and other international mechanisms do help create international "norms" that condemn the use of biological agents for state or non-state use as a weapon, it does not constitute a deterrent by itself. A verification regime could provide the global support for deterrent strategies if credible attribution were achieved. For such a regime to be credible, the uncertainties would need to be acknowledged and methods to address them formulated, tested, and institutionalized. While intellectually provocative and useful in strategic planning contexts, delineating lists of likely future biological weapons threats is a risky game at best. The reasonable and acceptable uncertainties of biological verification should be explored in more than a cursory way. The challenges and the real work are ultimately in the details of resolving the scope and structure.

[55] Gregory D. Koblentz, "The De Novo Synthesis of Horsepox Virus: Implications for Biosecurity and Recommendations for Preventing the Reemergence of Smallpox," *Health Security*, Dec. 2017, pp. 620-628, http://doi.org/10.1089/hs.2017.0061.
[56] Named for former Senators Sam Nunn of Georgia and Richard Lugar of Indiana, the Nunn-Lugar Cooperative Threat Reduction (CTR) programs were originally implemented to secure and dismantle weapons of mass destruction in states of the former Soviet Union.

The issue of a state (or in the lesser probability, a terrorist group) utilizing advanced biological weapons against another state is a mounting concern both in context of the current global pandemic and because of increased interest in biotechnology globally. Yet, little weapons deterrence research addresses methods of dealing with the threat of biological weapons and even less so with deterring bioterrorism. Bridging the gap between the life sciences and social sciences is crucial for devising implementable strategies that can lead to successful deterrence of bioweapons. Similarly, thinking about verification and international arms control regimes can be explored as part of new approaches to strategic deterrence in this century.

Looking Ahead

The potential applications of advanced gene editing techniques like CRISPR, and many of the challenges and pitfalls associated with the technology, are yet to be determined—particularly the national and international security implications. Governance that addresses such uncertainties, while not hindering research, is tough. Like other emerging technologies, the rate of innovation within the field outpaces that of regulations.

The rate and broad diffusion of emerging technology matters. There has not been sufficient time for institutions to form mechanisms that respond to and monitor the ways that humans combine gene editing and security challenges. Mechanisms include, but are not limited to, exploitation of advances in the life sciences and biotechnology for biological (as well as chemical) weapons proliferation. As such, this specific field needs more study in order to assess its level of threat to international security.

The dual-use conundrum applies to all modern technologies, but it has become a greater concern due to other characteristics in the changing strategic environment. Reducing the risk from misuse of technology will mean considering the increasingly transnational natures of the technologies.[57] In order to reduce the risks of malfeasant applications of biotechnology, both traditional and innovative new approaches to nonproliferation and counterproliferation are important policy elements. Efforts to strengthen existing international regimes to control transfers of dual-use materials and confidence building measures are also valuable.[58] Verification is

[57] Margaret E. Kosal, "Emerging Chemical and Biological Technologies: Security & Policy Challenges" in Tratras Contis et al.; *Responsible Conduct in Chemistry Research and Practice: Global Perspectives*, (American Chemical Society: Washington, D.C.), 2018, pp. 51-68.
[58] Anne-Yolande Bilala and Francisco Galamas, "A Bioterrorism Prevention Initiative: A Collaborative Approach," *The Nonproliferation Review,* vol. 22, (Nov. 2015), pp. 83-92; John Krige, "National Security and Academia: Regulating the international circulation of knowledge," *Bulletin of the Atomic Scientists*, vol. 70, no. 2 (2014), pp. 42-52; Margaret E. Kosal, "U.S. Policies to Reduce the Threat of Chemical Terrorism," in *9/11 + 6 Initiative Foreign Policy Priorities for a Secure America*, The Partnership for a Secure America, May 2008, http://www.psaonline.org/downloads/CHEMICAL%20report%208-28-08.pdf; Philippe

both a technical and a diplomatic challenge, which means that it is not the domain of any single disciplinary field or commercial sector. The role of international agreements and cooperative programs in the twenty-first century is a vibrant and contested intellectual and policy field.

As gene editing has broadened capabilities to misuse biology and research for malfeasant purposes, it may also provide solutions that have been long sought after in diagnostics, detection, and other areas. Applications of gene editing like the SHERLOCK and DETECTR technologies may hold the keys to address those challenges. In the case of the convergence between gene engineering and other technologies, the strengths of CRISPR-based detection tech need to be applied in the field to enhance prevention defense, response, mitigation, and deterrence.

In the race to create even more powerful gene editing technologies, we risk facing an international arms race, this time with biological technology. In order to avoid such escalation, nations should instead fund research into technologies like the SHERLOCK and DETECTR tests and the underlying basic and applied research that generates new discoveries and innovations.

The difference between beneficial and dangerous research is often only one of intent. Understanding politics, organizational structures, capability, capacity, and tacit knowledge are all necessary. The rate of scientific progress outpaces that of institutional frameworks, which is not new. As the realms of science, engineering, and technology forge into the future, so, too, should our ideas around governance. Our survival may depend on it.

Stroot and Ursula Jenal, "A New Approach: Contributing to BWC Compliance via Biosafety, Biosecurity, and Biorisk Management," *The Nonproliferation Review*, vol. 1, no. 18 (2011), pp. 545-555; and Iris Hunger and Shen Dingli, "Improving Transparency: Revisiting and Revising the BWC's Confidence-Building Measures," *The Nonproliferation Review*, vol. 18 (2011), pp. 513-552.